

CLAIMS

We claim:

1. A targeting construct comprising:
 - (a) a first polynucleotide sequence homologous to at least a first portion of a glucagon receptor gene;
 - (b) a second polynucleotide sequence homologous to at least a second portion of the glucagon receptor gene; and
 - (c) a selectable marker.
2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.
3. A method of producing a targeting construct, the method comprising:
 - (a) providing a first polynucleotide sequence homologous to at least a first portion of a glucagon receptor gene;
 - (b) providing a second polynucleotide sequence homologous to at least a second portion of the glucagon receptor gene;
 - (c) providing a selectable marker; and
 - (d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.
4. A method of producing a targeting construct, the method comprising:
 - (a) providing a polynucleotide comprising a first sequence homologous to a first region of a glucagon receptor gene, and a second sequence homologous to a second region of a glucagon receptor gene; and
 - (b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.
5. A cell comprising a disruption in a glucagon receptor gene.
6. The cell of claim 5, wherein the cell is a murine cell.
7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.
8. A non-human transgenic animal comprising a disruption in a glucagon receptor gene.
9. The non-human transgenic animal of claim 8, wherein the transgenic animal is a mouse.

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10. A cell derived from the transgenic mouse of claim 9.
 11. A method of producing a transgenic mouse comprising a disruption in a glucagon receptor gene, the method comprising:
 - (a) introducing the targeting construct of claim 1 into a cell;
 - (b) introducing the cell into a blastocyst;
 - (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
 - (d) breeding the chimeric mouse to produce the transgenic mouse.
 12. A method of identifying an agent that modulates the expression of a glucagon receptor gene, the method comprising:
 - (a) providing a non-human transgenic animal comprising a disruption in the glucagon receptor gene;
 - (b) administering an agent to the non-human transgenic animal; and
 - (c) determining whether the expression of the disrupted glucagon receptor gene in the non-human transgenic animal is modulated.
 13. A method of identifying an agent that modulates the function a glucagon receptor gene, the method comprising:
 - (a) providing a non-human transgenic animal comprising a disruption in a glucagon receptor gene;
 - (b) administering an agent to the non-human transgenic animal; and
 - (c) determining whether the function of the disrupted glucagon receptor gene in the non-human transgenic animal is modulated.
 14. A method of identifying an agent that modulates the expression of a glucagon receptor gene, the method comprising:
 - (a) providing a cell comprising a disruption in a glucagon receptor gene;
 - (b) contacting the cell with the agent; and
 - (c) determining whether the expression of the glucagon receptor gene is modulated.
 15. A method of identifying an agent that modulates the function of a glucagon receptor gene, the method comprising:
 - (a) providing a cell comprising a disruption in a glucagon receptor gene;

- (b) contacting the cell with the agent; and
- (c) determining whether the function of the glucagon receptor gene is modulated.
16. The method of claim 14 or claim 15, wherein the cell is derived from the non-human transgenic animal of claim 8.
 17. An agent identified by the method of claim 12, claim 13, claim 14, or claim 15.
 18. A transgenic mouse comprising a disruption in a glucagon receptor gene, wherein there is no significant expression of the glucagon receptor gene in the transgenic mouse.
 19. A transgenic animal comprising a disruption in a glucagon receptor gene, wherein the transgenic animal exhibits a high tolerance to a glucose challenge.
 20. The transgenic animal of claim 19, wherein the high tolerance to a glucose challenge is observed before and after exposure to a high-fat diet.
 21. A transgenic animal comprising a disruption in a glucagon receptor gene, wherein the transgenic animal exhibits lower fasting glucose levels, relative to a wild-type mouse.
 22. A transgenic animal comprising a disruption in a glucagon receptor gene, wherein the transgenic animal exhibits lower fasting insulin levels, relative to a wild-type mouse.
 23. A transgenic animal comprising a disruption in a glucagon receptor gene, wherein the transgenic animal exhibits increased glucagon levels, relative to a wild-type mouse.
 24. A transgenic animal comprising a disruption in a glucagon receptor gene, wherein the transgenic mouse gains less body weight, relative to a wild-type mouse.
 25. The transgenic mouse of claim 24, wherein the transgenic animal is subjected to a high-fat diet.
 26. The transgenic mouse of claim 25, wherein the transgenic animal consumes an approximately equivalent amount of food when compared to a wild-type mouse.
 27. A transgenic mouse comprising a disruption in a glucagon receptor gene, wherein the transgenic mouse exhibits abnormalities of the pancreas.

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28. The transgenic mouse of claim 27, wherein the abnormality comprises at least one of the following: hyperplasia, hypertrophy, increased cytoplasmic vacuolization, or increased cytoplasmic granularity.
29. The transgenic mouse of claim 28, wherein the abnormality is exhibited in adult animals and aged animals.
30. The transgenic mouse of claim 27, wherein the abnormality comprises an adenoma.
31. The transgenic mouse of claim 30, wherein the adenoma is exhibited in aged animals.
32. A transgenic mouse comprising a disruption in a glucagon receptor gene, wherein the transgenic mouse exhibits at least one of the following phenotypes: decreased fat as a percentage of body soft tissue, decreased body weight, decreased organ weight, or abnormal body shape.
33. A transgenic mouse comprising a disruption in a glucagon receptor gene, wherein the transgenic mouse exhibits infertility.
34. A cell derived from the transgenic mouse of claim 19, claim 21, claim 22, claim 23, or claim 24.
35. A method of producing a transgenic mouse comprising a disruption in a glucagon receptor gene, the method comprising:
 - (a) introducing a glucagon receptor gene targeting construct into a cell;
 - (b) introducing the cell into a blastocyst;
 - (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
 - (d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a glucagon receptor gene, wherein the transgenic mouse exhibits one of the following phenotypes: increased glucose tolerance, decreased serum glucose levels, decreased serum insulin levels, increased glucagon levels, decreased body weight gain, an abnormality of the pancreas, abnormalities in body weight, organ weight or body shape, decreased body fat percentage, or infertility.
36. A method of identifying an agent that ameliorates a phenotype associated with a disruption in a glucagon receptor gene, the method comprising:

- (a) administering an agent to a transgenic mouse comprising a disruption in a glucagon receptor gene; and
 - (b) determining whether the agent ameliorates at least one of the following phenotypes: increased glucose tolerance, decreased serum glucose levels, decreased serum insulin levels, increased glucagon levels, decreased body weight gain, an abnormality of the pancreas, abnormalities in body weight, organ weight or body shape, decreased body fat percentage, or infertility.
37. A method of identifying an agent which modulates glucagon receptor gene expression or function, the method comprising:
- (a) administering an agent to the transgenic mouse comprising a disruption in a glucagon receptor gene; and
 - (b) determining whether the agent modulates glucagon receptor gene expression or function in the transgenic mouse, wherein the agent has an effect on at least one of the following: increased glucose tolerance, decreased serum glucose levels, decreased serum insulin levels, increased glucagon levels, decreased body weight gain, an abnormality of the pancreas, abnormalities in body weight, organ weight or body shape, decreased body fat percentage, or infertility.
38. A method of identifying an agent which modulates glucagon receptor gene expression or function, the method comprising:
- (a) providing a cell comprising a disruption in a glucagon receptor gene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether the agent modulates glucagon receptor gene expression or function, wherein the agent modulates one of the following phenotypes: increased glucose tolerance, decreased serum glucose levels, decreased serum insulin levels, increased glucagon levels, decreased body weight gain, an abnormality of the pancreas, abnormalities in body weight, organ weight or body shape, decreased body fat percentage, or infertility.
39. The method of claim 38, wherein the cell is derived from the transgenic animal of claim 5.
40. An agent identified by the method of claim 36, claim 37, or claim 38.
41. An agonist or antagonist of a glucagon receptor.

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42. An agent that modulates the function, expression or activity of a glucagon receptor gene.
 43. A method of ameliorating a condition associated with impaired glucose tolerance, the method comprising administering to a subject in need a therapeutically effective amount of an agent that modulates glucagon receptor function, expression or activity.
 44. A method of identifying an agent that inhibits the activity or function of a glucagon receptor, the method comprising:
 - (a) providing a cell expressing the glucagon receptor gene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether the agent inhibits the activity or function of the glucagon receptor, wherein the agent has an affect on one or more of the following: glucose tolerance, glucose levels, insulin levels, glucagon levels, body fat percentage, or body weight gain.
 45. The method of claim 44, wherein the cell is obtained from a human diabetic cell line.
 46. The method of claim 44, wherein the glucagon receptor gene comprises a human glucagon receptor gene.
 47. The method of claim 46, wherein the human glucagon receptor gene comprises SEQ ID NO:5.
 48. A method of identifying an agent that has an affect on obesity or weight gain, the method comprising:
 - (a) providing a mouse expressing a glucagon receptor gene;
 - (b) subjecting the mouse to a high-fat diet;
 - (c) administering a putative agent to the mouse; and
 - (d) determining whether the putative agent has an affect on weight gain or body fat percentage in the mouse.
 49. A method of identifying an agent that has an affect on obesity or weight gain, the method comprising:
 - (a) providing a cell expressing a glucagon receptor gene;
 - (b) contacting the cell with a putative agent; and

- (c) determining whether the agent has an affect on one of the following: fat accumulation or cell size.
50. The method of claim 49, wherein the cell is an adipose cell.
51. A method of identifying an agent that has an affect on diabetes or diabetic conditions, the method comprising:
- (a) providing a mouse expressing a glucagon receptor gene;
 - (b) administering a putative agent to the mouse; and
 - (c) determining whether the putative agent has an affect on one of the following: glucose tolerance, glucose levels, glucose uptake, insulin levels, insulin sensitivity, or insulin secretion.
52. A method of identifying an agent that has an affect on diabetes or diabetic conditions, the method comprising:
- (a) providing a cell expressing a glucagon receptor gene;
 - (b) contacting the cell with a putative agent; and
 - (c) determining whether the agent has an affect on one of the following: glucose tolerance, glucose uptake, insulin sensitivity, or insulin secretion.
53. The method of claim 52, wherein the cell is one of the following: a muscle cell, an adipose cell, a liver cell, or a pancreas cell.
54. A method of treating obesity, the method comprising administering a therapeutically effective amount of an antagonist of a glucagon receptor.
55. A method of treating diabetes or diabetic conditions, the method comprising administering a therapeutically effective amount of an antagonist of a glucagon receptor.
56. Phenotypic data associated with a transgenic mouse comprising a disruption in a glucagon receptor gene, wherein the phenotypic data is in an electronic database.

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